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Association of liver biomarkers in T2DM patients, Northern Ethiopia: A cross-sectional study

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Abstract

Background

Liver disease, Non-Alcoholic Fatty Liver Disease (NAFLD) in particular, is a considerable cause of morbidity and mortality among patients with type 2 diabetes mellitus. Mounting evidence demonstrated that monitoring liver function biomarkers is critical for early detection and control of the disease. However, this relationship is not evaluated in the study setting.

Objectives

To determine the association of liver biomarkers in T2DM Patients, Northern Ethiopia, from March 2020 to June2020.

Methods

A hospital-based cross-sectional study was conducted from March to June, 2020 among 331 type 2 diabetes mellitus patients. Lifestyle and socio-demographic data were collected through interviews with the participants. Clinical data were reviewed from the medical record. Anthropometric measurements were taken following WHO protocol. Liver function markers were measured using an automated chemistry analyzer. The data was entered and analyzed using SPSS version 23. Categorical variables were presented using frequencies and percentages. Quantitative variables were described using means and standard deviations. Binary and multivariate logistic regressions were used to identify factors associated with liver function abnormalities.

Results

A total of 331 (52.6% males) type 2 diabetes mellitus patients participated in this study. The mean fasting blood sugar level was 183±10.4mg/dl. Overall, 40% of the participants had abnormal liver function. In the multivariate analysis, male sex (AOR = 2.48; 95% CI: 1.43–4.31), duration of disease since diagnosis ≤5 years (AOR = 2.94; 95% CI: 1.30–6.63), alcohol intake (AOR =3.90, 95%CI:1.98-7.66), waist circumference (AOR = 3.81; 95% CI: 1.85-7.83), BMI ≥ 30kg/m2 (AOR = 3.96; 95% CI: 1.40–11.15), and FBS >200 mg/dl (AOR = 4.84; 95% CI: 1.33–17) were significantly associated with liver function abnormalities.

Conclusions

Liver function abnormalities were common among T2DM patients at Ayder Comprehensive Specialized Hospital. Sex, disease duration, BMI, waist circumference, alcohol intake and fasting blood sugar were significant contributors for the observed liver biomarker derangement.

Key words: type 2 diabetes mellitus, liver function, Ethiopia

Introduction

Liver disease is a considerable cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM) [1]. Among others, Non-Alcoholic Fatty Liver Disease (NAFLD) secondary to insulin resistance (IR) is an established etiology in these groups [2]. Substantiating this evidence, literature demonstrated that ultrasound-confirmed NAFLD is apparent on 42-70% of persons with T2DM [3]. And diabetic patients with NAFLD are at increased risk for advanced liver diseases, cirrhosis and hepatocellular carcinoma [4]. Further making the situation more attention drawing, mortality due to NAFLD induced cirrhosis in T2DM subjects is even greater than T2DM mediated cardiovascular deaths [5]. Thus, liver disease is an overlooked but devastating complication of T2DM that needs an attention that it deserves [6]. Remission of NAFLD is possible through investment on physical activity, hypo-caloric diets to correct obesity and proper intake of diabetic medications to control glycemia [7]. However, most of the patients with T2DM do not manifest any overt signs and symptoms until the NAFLD reaches advanced stages [8]. Hence, the condition is threatening the life of T2DM patients in silence. Existing evidence suggest that liver disease together with T2DM constitute an increased risk for cardiovascular disease [9, 10] and renal failure [11]. This makes early detection of NAFLD among patients with T2DM imperative not only for prevention of hepatic complications but also avert cardiovascular diseases and renal dysfunction. Liver biopsy to assess histopathological changes associated with NAFLD and its advanced forms is the gold standard for diagnosis. However, high cost and potential adverse events associated with the biopsy technique preclude its use as a surveillance method [12]. Alternatively, evolving evidence suggests that a strong link exists between liver biomarkers and poorly controlled diabetes mellitus [13]. Raised serum concentrations of transaminases enzymes correspond to seepage of hepatic intracellular enzymes into the circulation [14]. Thus, alterations in liver biomarkers are considered as surrogate markers of hepatic injury in NAFLD [15]. Determining these biomarkers among diabetic patients will help in the early detection and management of potential liver diseases. However, studies documenting these biomarkers are scarce in the present study areas. Therefore, this study was aimed to evaluate liver biomarkers among type 2 diabetes mellitus and its purpose to early detection and management of liver complications in those patients.

Materials and Methods

Study area

This study was conducted in Ayder comprehensive specialized Hospital, Mekelle, Tigray region, North Ethiopia. Mekelle is located 780 kilometers to the north from the capital, Addis Ababa. Ayder Comprehensive Specialized hospital (ACSH) is a tertiary teaching hospital which provides a service for both out-and-in patients. It has about 500 inpatient beds and provides various specialty and subspecialty services to the community in its catchment: Tigray, Afar and Northeastern parts of Amhara. The out-patient service at the Diabetic Clinic is well organized, staffed with physicians and expert nurses in diabetic care [16].

Study design and period

This was a hospital-based cross-sectional study conducted from March 2020 to June 2020.

Study participants

The participants of this study were T2DM patients who have follow-up at ACSH Diabetic clinic. Patients with known chronic illnesses other than T2DM, taking hepatotoxic drugs, mothers using oral contraceptives or those who are pregnant or lactating were excluded.

Sample size and sampling technique

Sample size was estimated considering 48.4% AST abnormality among type 2 DM patients in Gondar [17]. We used single proportion formula to attain a sample size of 331 taking 5% margin of error (d), reliability coefficient Z = 1.96 at 95% confidence interval and 10% non-response rate in to account. Moreover, since the population size in the study area was less than 10,000; a population correction factor was employed. Convenient sampling technique was applied to recruit consecutive participants for the study.

Data Collection Techniques

Interviewer administered questionnaire was used to obtain information on socio-demographic and lifestyle matters. Clinical data was obtained from patient's medical records. Anthropometric (weight, height, waist circumference) and blood pressure measurements were done according to WHO guideline by trained nurses. Body mass index (BMI) was calculated as weight in Kg divided by height in meter squared (kg/ m^2) [18]. Moreover, about 5 milliliter of venous blood was drawn on serum separating tubes (SST) from each participant and allowed to clot for 30 minutes. Finally the clotted sample was centrifuged at 2000 RMP for 5 minutes and the serum extract was investigated for the level of liver biomarkers; AST, ALT, ALP, GGT, as well as total and direct bilirubin.

Data Management and Quality Assurance

To assert the quality of data the questionnaire was prepared first in English then translated to study subject's mother tongue (Tigrigna). Training was given to data collectors and supervisors before data collection. Moreover, the laboratory analysis was carried out in a properly calibrated clinical chemistry analyzer with controls running along sides the subject sample for validating the process in accordance with the standard operation procedure and manufacturer's instructions. Collected results were checked for completeness and quality on daily basis by the immediate supervisor.

Data Analysis

After checking for completeness and consistency of the collected information, the data was entered and analyzed using SPSS version 23.0 software package. Frequency distribution and percentages were used to describe different categorical variables. Measures of central tendency and dispersion were used to describe continuous variables. Bivariate analysis was performed to show the association between dependent and independent variables and variables with p-value $\leq$ 0.25 were transferred to the multivariable analysis to assess possible confounders. P-value < 0.05 was used to declare statistical significance.

Results

The study included 331 T2DM patients, with 174 (52.6%) males and 157 (47.4%) females. The average age of the study participants was 54.9 years (5.8 $\pm$SD). More than half of the patients, 187 (56.5%), were uneducated. The vast majority of them (60.4%) drank coffee. Approximately 178 (53.8%) of them were physically active, and none of them smoke cigarette. Nearly 127 (38.4%) of the participants control their diabetes through medicine and diet, Table 1.

In terms of clinical characteristics, the study participants' mean systolic and diastolic blood pressures were 124.5$\pm$14.8 mmHg and 75$\pm$9.1 mmHg, respectively. Similarly, 125 (37.8%) had systolic blood pressure $\geq$140 mmHg while the other 42 (12.7%) had diastolic blood pressure $\geq$ 90 mmHg. The average duration of T2DM since diagnosis was 8$\pm$3.7 years, of which 158 (47.7%) lived 6-10 years. Mean waist circumference of the study groups was 82$\pm$11.4, where 57 (17.2%) of them had central obesity. The mean BMI was 23.8$\pm$3 kg/m^2, with 111 (33.5%) and 29 (8.8%) of them classified as overweight (25-29.9 kg/m^2) and obese (>30 kg/m^2, respectively. With regard to their fasting blood sugar (FBS) level, the average FBS was 183$\pm$10.4mg/dl of which 96 (29.0%) and 65 (19.6%) of them had fasting blood sugars of 140-200 mg/dl and >200 mg/dl ranges, respectively, [Table 1].

Table 1: Socio Demographic and lifestyle related variables of study subjects

Study variable Category	Frequency, n (%)
Sex	
Female	157(47.4)
Male	174(52.6)
Age	
<55	180(54.4)
>55	151(45.6)
Education status	
No formal education	187(56.5)
Primary	48(14.5)
Secondary	47(14.2)
College and above	49(14.8)
Controlling Method	
Diet, exercise , medication	27(8.2)
Exercise and medication	86(26.0)
Diet and medication	127(38.4)
Medication only	91(27.5)
Medications taken for T2DM treatment	
Insulin	38(11.5)
Metformin	118(35.7)
Metformin + Glibenclamide	77(23.3)
Glibenclamide	98(29.6)
Duration of disease	
>11	97(29.3)
6-10	158(47.7)
<5	76(23.0)

Table 1: Socio Demographic and lifestyle related variables of study subjects continued...

Study variable Category	Frequency, n (%)
Alcohol intake	
Alcoholic	135 (40.8)
Non-alcoholic	246 (59.2)
Coffee intake	
Yes	200(60.4)
No	131(39.6)
Physical activity	
Yes	178(53.8)
No	153(46.2)

The most frequently deranged liver function biomarker was ALT, 122 (36.9%), followed by AST, 92 (27.8%). [Table2]

Table 2: Average values and proportions of abnormalities in each liver biomarker

Biochemical parameter	Mean ±SD	Patients with abnormal biochemical parameter, n (%)
ALT	40.4±25.2	122(36.9)
AST	32.4±20.3	92(27.8)
GGT	34.8±16.4	33(10)
Total bilirubin	0.59±1.6	24(7.3)
Direct bilirubin	0.13±0.05	9(2.7)

ALT (Alanine transaminase), AST (Aspartate transaminase), GGT (gamma-glutamyl transferase, SD (standard deviation)

Aggregate proportion of liver biomarker abnormalities

Out of the 331 T2DM patients, 132 (40.0%) had one or more abnormal liver biomarkers where 87 (26.3%) had at least two, and 7 (2.1%) had all biomarkers abnormal.

Factors associated with Liver biomarker abnormality among T2DM patients

Both bivariate and multivariate analyses were performed to identify factors associated with the observed liver function abnormality. In the bivariate analysis, sex (COR=1.81, 95% CI:1.15, 2.83), age (COR=1.48, 95% CI:0.95, 2.31), duration of T2DM (COR=2.15, 95%, CI:1.16, 3.98), coffee intake (COR=1.42, 95% CI:0.91, 2.23), alcohol intake (COR=4.02, 95%CI: 2.39-6.76) physical activity (COR=1.35, 95% CI:0.87, 2.10), BMI (COR=6.17, 95%CI:2.58, 14.74), waist circumference (COR=3.48, 95%CI:1.91, 6.34), systolic blood pressure (COR=1.38, 95% CI:0.88, 2.18), diastolic blood pressure (COR=1.60, 95% CI:0.83, 3.07), blood sugar controlling method (COR=0.93, 95% CI:0.39, 2.20), and FBS (COR=2.69, 95%CI:1.49-4.83), were significantly associated with the outcome variable at $p \leq 0.25$, Table 3.

However, in the multivariate analysis, only sex of patients (AOR=2.48,95%CI:1.43,4.31), disease duration since diagnosis (AOR=2.94,95%CI:1.30,6.63), alcohol intake (AOR =3.90, 95%CI:1.98-7.66), waist circumference (AOR=3.81, 95%CI: 1.85, 7.83), BMI (AOR=3.96, 95%CI: 1.40, 11.15), and FBS (AOR=4.84, 95%CI: 1.33, 17.65) of patients were able to retain significant association with the observed liver biomarker abnormalities at $p<0.05$, [Table 3 and Figure 1 &2].

Table 3 Bivariate and multivariable analysis of factors associated with liver biomarker abnormality among T2DM patients.

Study variables	Category	Abnormal liver function		COR(95%CI)	AOR(95%CI)	P-value
		Yes (%)	No (%)			
Sex	Male	81(46.6)	93(53.5)	1.81(1.15-2.83)	2.48(1.43-4.31)	**0.001**
	Female	51(32.5)	106(67.5)	1.00	1.00	
Age	>55	68(45.0)	83(55.0)	1.48(0.95-2.31)	1.46(0.82-2.60)	0.196
	<55	64(35.6)	116(64.4)	1.00	1.00	
Duration of T2DM since diagnosis	<5	40(52.6)	36(47.4)	2.15(1.16-3.98)	2.94(1.30-6.63)	**0.009**
	6-10	59(37.3)	99(62.7)	1.15(0.68-1.96)	1.72(0.91-3.26)	0.092
	>11	33(34.0)	64(66.0)	1.00	1.00	
Alcohol intake	Alcoholic	55(64.7)	30(35.3)	4.02(2.39-6.76)	3.90(1.98-7.66)	**0.000**
	Non-alcoholic	77(31.3)	169(68.7)	1.00	1.00	
Coffee Drink	No	59(45.0)	72(55.0)	1.42(0.91-2.23)	1.22(0.67-2.21)	0.507
	Yes	73(36.5)	127(63.5)	1.00	1.00	
Physical exercise	No	67(43.8)	86(56.2)	1.35(0.87-2.10)	1.58(0.85-2.94)	0.146
	Yes	65(36.5)	113(63.5)	1.00	1.00	
BMI	Obese	21(72.4)	8(27.6)	6.17(2.58-14.74)	3.96(1.40-11.15)	**0.009**
	Over weight	54(48.6)	57(51.4)	2.22(1.37-3.61)	1.60(0.89-2.85)	0.111
	Normal	57(29.9)	134(70.1)	1.00	1.00	
Waist circumference	Central obesity	37(64.9)	20(35.1)	3.48(1.91-6.34)	3.81(1.85-7.83)	**0.000**
	Normal	95(34.7)	179(65.3)	1.00	1.00	
Systolic blood pressure(BP)	>140 mmHg	56(44.8)	69(55.2)	1.38(0.88-2.18)	1.35(0.76-2.38)	0.295
	<140 mmHg	76(36.9)	130(63.1)	1.00	1.00	
Diastolic BP	>90 mmHg	21(50)	21(50)	1.60(0.83-3.07)	1.40(0.60-3.25)	0.432
	<90 mmHg	111(38.4)	178(61.6)	1.00	1.00	
Fasting blood sugar	>200mg/dl	37(56.9)	28(43.1)	2.69(1.49-4.83)	4.84(1.33-17.7)	0.017
	140-200mg/dl	39(40.6)	57(59.4)	1.39(0.83-2.33)	2.75(1.09-6.97)	0.032
	<140mg/dl	56(32.9)	114(67.1)	1.00	1.00	
Controlling Method	Medication only	47(51.7)	44(48.4)	1.81(0.75-4.39)	1.30(0.27-6.17)	0.734
	Diet, medication	45(35.4)	82(64.6)	0.93(0.39-2.20)	1.94(0.57-6.52)	0.282
	Exercise and medication	30(34.9)	56(65.1)	0.91(0.37-2.23)	0.80(0.26-2.41)	0.698
	Diet, exercise, medication	10(37.0)	17(63.0)	1.00	1.00	

Note: COR-Crude Odds Ratio, AOR-Adjusted odds Ratio, CI-Confidence interval, BMI-Body mass index

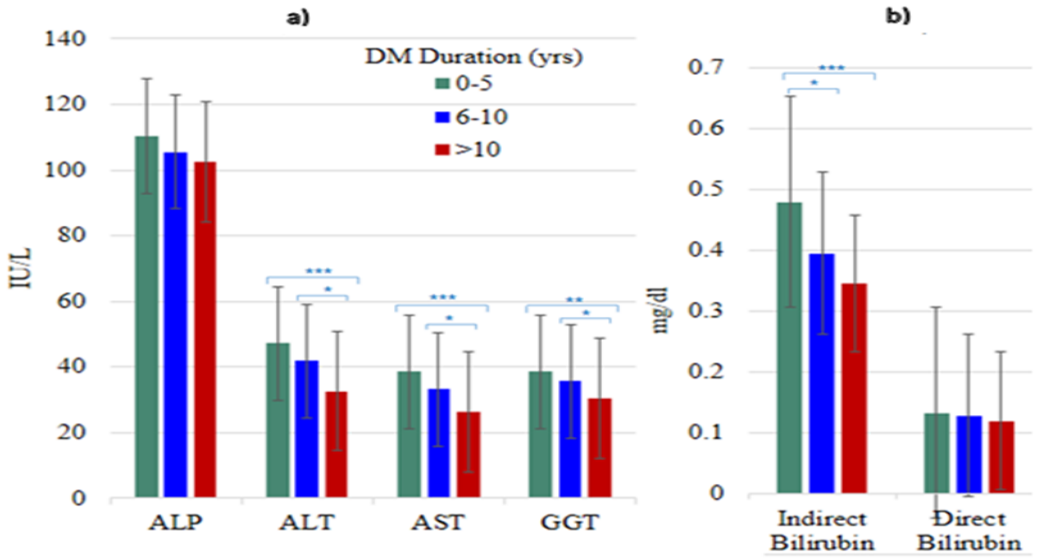

Figure 1: Pattern of liver biomarker abnormalities across categories of duration of T2DM

**** means P<0.001; ** 0.001<P<0.01; * 0.01<P<0.05. ALT (Alanine transaminase), AST (Aspartate transaminase), GGT (gamma-glutamyl transferase), ALP (Alkaline Phosphatase), DM (diabetes Mellitus)*

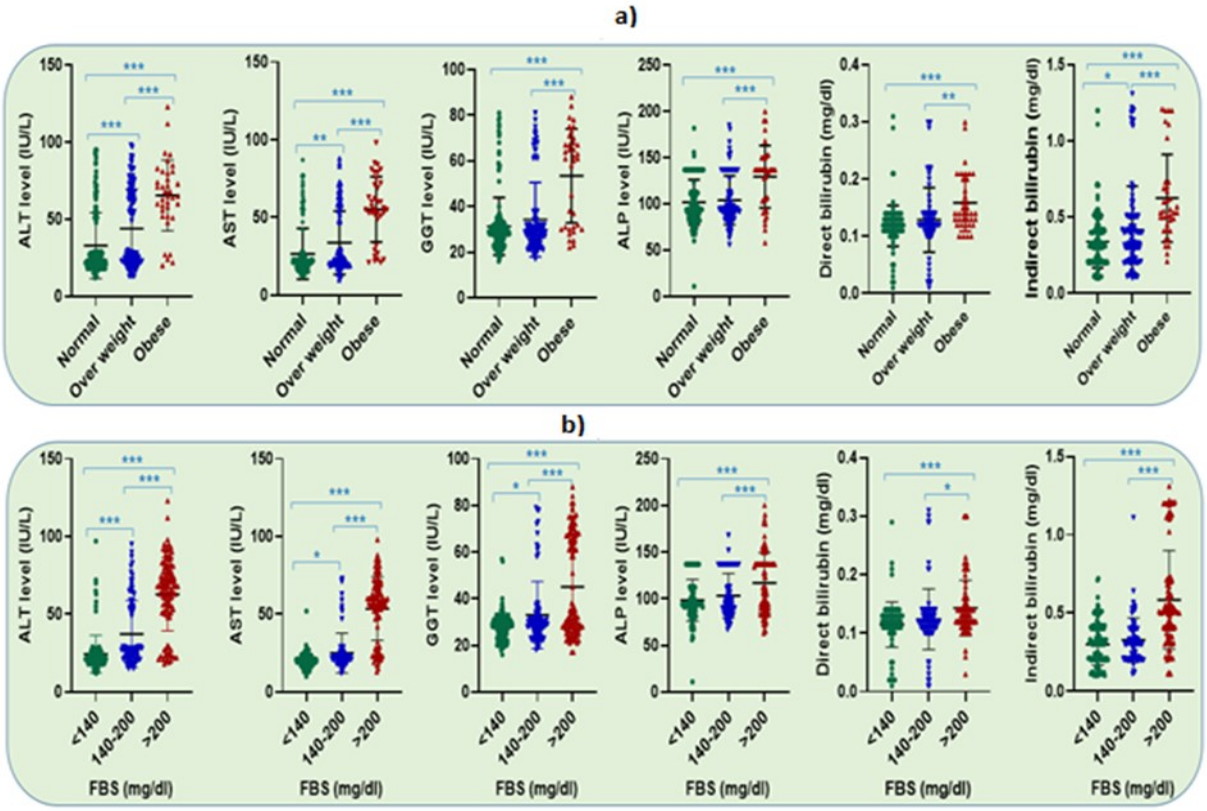

Figure 2: Pattern of liver biomarkers abnormality across categories of BMI and FBS

**** means P<0.001; ** 0.001<P<0.01; * 0.01<P<0.05. ALT (Alanine transaminase), AST (Aspartate transaminase), GGT (gamma-glutamyl transferase), ALP (Alkaline Phosphatase), FBS (Fasting blood sugar), DM (diabetes Mellitus)*

Discussion

This study aimed to assess the liver biomarkers status among T2DM patients at Ayder Comprehensive Specialized Hospital. The findings showed that 40% of the studied patients had at least one liver biomarker abnormality while about 26% had two or more abnormal biomarkers. ALT (36.9%) was the most common deranged biomarker. Sex, alcohol consumption, duration of T2DM, waist circumference, BMI, and FBS level were factors that revealed a significant association with the recorded Liver biomarkers derangement.

The 40% prevalence of abnormalities in at least one Liver function test (LFT) in the current study is consistent with a finding from South Africa (42%) [19]. It is; however, lower than the figures from Western Ethiopia, Jimma (57.7%) [20], Bangladesh (61.2%) [21], North India (62.53%] [22], and Northeast India (71.25%] [23]. In contrast, it is greater than the reports North Ethiopia, Gondar (33.3%) [24], Sudan (22%) [25] and Finland (27%) [26]. Despite the noteworthy derangement of liver function tests among T2DM patients in all studies, there are variations in the magnitude. Regarding Ethiopia, the increased proportion from Jimma compared with the findings in this study and Gondar could be attributable to the community's Khat chewing habit, where cathinone and cathine-induced liver damage is suspected [27]. Variations in the cutoff values chosen due to differences in the studied populations' sociodemographic characteristics (such as age and ethnicity) could potentially be a plausible explanation for the inconsistencies observed between the nations [28].

The current study's 26% rate of having two or more abnormalities is consistent with the findings of Elmahi H and Abdrabo A in Sudan (24) [25] and Salmela PI et al. in Finland (27%) [26]. However, it is greater than the Gondar's figure (18.9%) [24]. Similarly, the major ALT derangement (39.6%) seen in the current study is consistent with the primary increases in ALT among study participants from Gondar (23.3%) [24], Bangladesh (18%) [29], Nepal (40.4%) [30] and North West Ethiopia (40.1%) [17]. However, this contradicts the findings of another study conducted in Bangladesh, where the primary derangement was detected in the AST value (AST 34.1% versus ALT 19%) [21]. This could be related to differences in the mean length of diabetes in the study participants, as ALT levels fall with time rather than AST levels, yet neither paper specifies the typical duration of diabetes in their study subjects.

Sex was shown to be substantially linked with abnormal liver function tests (liver biomarkers) in this study. Male participants were 2.48 times more likely than females to have abnormal liver function tests. This is consistent with studies that have found a link between male sex and aberrant LFTs [31-33]. However, it differs from previous research that found no significant link between sex and liver function tests in T2DM patients [19, 34]. The gender difference in Liver biomarkers abnormalities may be explained by changes in body fat distribution caused by estrogen in females. In women of reproductive age, estrogen stimulates subcutaneous fat growth while decreasing visceral fat accumulation. This reduces the movement of fatty acids from visceral tissues to the liver, which helps to prevent NAFLD-mediated liver damage [35].

Insulin resistance, the primary source of hyperglycemia and compensatory hyperinsulinemia, is thought to be the leading cause of liver damage. This unhealthy association has multiple proposed routes. Insulin resistance leads to lipolysis in peripheral adipocytes. Free fatty acids are then released into the bloodstream and eventually accumulate in the liver. Concurrently, the fatty liver produces adipocytokines, which increase hepatocyte destruction by increasing oxidative stress in the cells. The combination of mitochondrial oxidative stress, hyperinsulinemia, and hyperglycemia produces free radicals causes inflammation and cellular necrosis. This is frequently accompanied by the subsequent seepage of liver contents into the bloodstream [36]. In support of the aforementioned biochemical phenomenon, abnormalities in liver biomarkers were found to increase with increasing fasting blood sugar (FBS) in the present study. The odds of experiencing LFT abnormality among patients with FBS >200 mg/dl and FBS of 140–200 mg/dl were 4.5 and 2.75 times higher than those with FBS <140mg/dl, respectively. This is in agreement with the data of Bora et al. [23], but not with the findings of Ayesha et al., who found no link [37].

Body mass index is one of the classical epidemiological indexes for assessing Obesity [38]. Obesity, in particular central obesity, is the strongest risk factor for NAFLD [39]. Previous studies demonstrated that, compared to those with a normal BMI, subjects with a higher BMI had a 4.1- to 14-fold increased risk for fatty liver [40]. Similarly, owing to the increased NALFD risk, it has been again indicated that obese subjects had more frequent LFT derangements than non-obese ones [41]. Akin to these concepts, type 2 diabetes patients in the current study had liver biomarker abnormalities that got worse across increasing BMI categories. T2DM patients with a BMI of ≥30 kg/m^2 were 3.96 times more likely to have abnormal liver function than T2DM patients with a BMI of 18–24.9 kg/m^2. This is consistent with other studies that claimed a raised LFT test with a higher BMI [42, 43]. Oxidative stress-mediated inflammation and cell necrosis associated with increased hepatic flow of fatty acids from the adipose tissues of such obese individuals are the suggested reasons for the observed derangement in the level of liver enzymes [44].

Another factor related with liver function test abnormalities reported in the current study was the duration of diabetes. Consistent across all biomarkers, the plasma levels decreased with increasing duration of T2DM. According to the data, the odds of observing abnormal liver biomarkers among patients who stayed with T2DM for five years or less were almost three times higher than those who lived for eleven years or more. This is linked between shorter duration of T2DM and abnormal liver function test is consistent with the findings of similar studies from Ethiopia [20, 24], Sudan [25], the United Kingdom [45], and Italy [46]. However, it contradicts with other reports that found no link between the duration of diabetes and liver function biomarkers [19, 37]. The inverse linkage between DM duration and liver function biomarkers may be attributed to a progressive drop in transaminase levels as the liver disease progresses to chronicity and/or liver cirrhosis [47]. It could also be related to survival bias, in which persons with severe conditions die sooner, especially in the case of the bilirubin molecules.

Liver biomarkers are therefore found affected in type 2 diabetes mellitus patients especially in earlier years of T2DM disease. Therefore, routine assessment of liver function tests could help early diagnosis and management of hepatic and other complications in type 2 Diabetes Mellitus patients.

Declarations

Ethical considerations

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Mekelle University College of Health Sciences (20/03/2020).

Abbreviations and acronyms

ACSH:- Ayder Comprehensive Specialized Hospital

ALP:- Alkaline phosphatase; ALT:- Alanine transaminase; AOR :- Adjusted Odds Ratio; AST:- Aspartate transaminase; BMI:- Body Mass Index; CI:- confidence Interval; COR :- Crude Odds ratio; DM :- Diabetes Mellitus; FBS :- Fasting Blood sugar; GGT :- Gamma Glutamyl transaminase; LFT :- Liver Function Test;

NALFD :- Non-alcoholic Fatty Liver Disease; RPM :- revolution per minute; SD :- Standard Deviation; SST :- Serum separating tubes; T2DM :- Type 2 Diabetes Mellitus; WHO :- World Health Organization;

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Availability of Data

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Authors' Contribution

Investigation, Project administration, and Software: Rigat Alem Abrha; Conceptualization, Methodology, validation, Supervision: Rigat Alem Abrha, Desalegn Teklu, Wegen Beyene Tesfamariam and Gebrekidan Gebregzabher Asfeha; Data Curation, Writing - Original Draft, Review & Editing: Rigat Alem Abrha, Desalegn Teklu, Wegen Beyene Tesfamariam, Gebrekidan Gebregzabher Asfeha, Hagos Amare Gebreyesus, Abrha Gebreselama Gebrehiwot.

Reference

1. Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus. Hepatobiliary Surg Nutr. 2015; 4(2):101-8.
2. Smith BW, Adams LA. Nonalcoholic fatty liver disease and diabetes mellitus: pathogenesis and treatment. Nat Rev Endocrinol. 2011; 7(8):456-65.
3. Williamson RM, Price JF, Glancy S, Perry E, Nee LD, Hayes PC, Frier BM, et al; Edinburgh Type 2 Diabetes Study Investigators. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care. 2011; 34(5):1139-44.
4. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004; 126(2):460-8.
5. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002; 346(16):1221-31.
6. Rao K.V.N. Mallikarjuna, Pusapati Surya Meenakshi, Kumar N. laxmana. Evaluation of Serum Transaminases in Type 2 Diabetes Mellitus. Indian Journal of Mednodent and Allied Sciences 2016; 4(3): 107-111
7. Medina J, Fernández-Salazar LI, García-Buey L, Moreno-Otero R. Approach to the pathogenesis and treatment of nonalcoholic steatohepatitis. Diabetes Care. 2004; 27(8):2057-66.
8. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001; 50(8):1844-50.
9. Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. Hepatology. 2006; 43(5):1145-51.
10. Targher G, Betolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of non-alcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007; 30:1212–8.
11. Targher G, Bertolini L, Rodella S, Zoppin G, Lippi G, Day C, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative or laser-treated retinopathy in type 2 diabetic patients. Diabetologia 2008; 51:444–50.
12. Nascimbeni F, Pais R, Bellentani S, Day CP, Ratziu V, Loria P et al. From NAFLD in clinical practice to answers from guidelines. J Hepatol. 2013; 59(4):859-71.
13. Odewabi A.O, Akinola E.G, Ogundahunsi O.A. Oyegunle, V., Amballi, A., Raimi, T., et al. Liver Enzymes and its correlates in treated and newly diagnosed type 2 diabetes mellitus patients in Osogbo, South West Nigeria. Asian J. Med. Sci., 2013; 5(5): 108-112,
14. Sunitha S, Gandham R, Wilma DS, Rao S. Evaluation of significance of liver enzymes as screening tests for the early detection of clinically asymptomatic non-alcoholic fatty liver disease in type 2 diabetes mellitus patients. Int J Biomed Adv Res. 2015; 6(12):860–3.
15. Raiza Phillip, Michelle Mathias, Sucheta Kumari N, Damodara Gowda K.M, Jayaprakash Shetty K. Evaluation of relationship between markers of liver function and the onset of type 2 diabetes. *Nitte University Journal of Health Science* 2014; 4(2): 90-93.
16. Referral hospital. Available on: http://www.mu.edu.et/chs/index.php/about-us. Accessed on 24 February 2019.
17. Shibabaw T, Dessie G, Molla MD, Zerihun MF, Ayelign B. Assessment of liver marker enzymes and its association with type 2 diabetes mellitus in Northwest Ethiopia:Journal of biomedical science. 2017;12(1):707-15
18. Onis M, Habicht J.Anthropometric reference data for international use: recommendation fromWorld Health Organization Expert Committee. The American journal of clinical nutrition. 2008;64(4):650-8.
19. Paruk IM, Pirie FJ, Motala AA, Kolawole BA. High prevalence of abnormal liver enymes in patients with type 2 diabetes mellitus attending a diabetes clinic. JEMDSA 2011;16(1):43-47
20. Bekele S, Cheneke W, Mekonnen Z. Assessment of Liver Function Tests and Associated Risk Factors Among Diabetic Patients Attending Diabetes Clinic of Jimma University Specialized Hospital, Jimma,Ethiopia. J Pharm Biomed Sci 2015 Feb; 05(02) Suppl:S25-S33.24.
21. Islam S, Rahman S, Haque T, Sumon AH, Ahmed AZM, Ali N. Prevalence of elevated liver enzymes and its association with type 2 diabetes: A cross-sectional study in Bangladeshi adults. Endocrinol *Diab Metab*. 2020; 3(2):e00116.
22. Alam S, Raghav A, Reyaz A, Ahsan A, Ahirwar AK, Jain V et al. Prevalence of elevated liver enzymes and its relationship with type 2 diabetes mellitus in North Indian adults. Metabol Open. 2021; 12:100130.
23. Bora K, Borah M, Chutia H, Nath CK, Das D, Ruram AA. Presence of concurrent derangements of liver function tests in type 2 diabetes and their relationship with glycemic status: A retrospective observational study from Meghalaya. J Lab Physicians 2016; 8:30-5.
24. Teshome G, Ambachew S, Fasil A, Abebe M. Prevalence of Liver Function Test Abnormality and Associated Factors in Type 2 Diabetes Mellitus: A Comparative Cross-Sectional Study. EJIFCC. 2019 Oct 11; 30(3):303-316. PMID: 31695587; PMCID: PMC6803769.

25. Elmahi H, Abdrabo A. Determinants of abnormal liver function tests in Diabetes Type 2 patients in Sudan. Jour-nal of Science. 2014; 4(1):45-9.
26. Salmela PI, Sotaniemi EA, Niemi M, Mäentausta O. Liver function tests in diabetic patients. Diabetes care. 1984; 7(3):248-54.
27. Coton T, Simon F, Oliver M, Kraemer P. Hepatotoxicity of khat chewing. Liver Int 2011;31: 434
28. Siest G, Schiele F, Galteau M-M, Panek E, Steinmetz J, Fagnani F, et al. Aspartate aminotransferase and alanine aminotransferase activities in plasma: statistical distribu-tions, individual variations, and reference values. Clinical chemistry. 1975; 21(8):1077-87.
29. Rashid MHO, Haque MZ, Rahman MK, Khan MMR, Rahman ASMM, Al-Mahtab M et al. Study on Liver Dysfunction in Type 2 Diabetic Patients in Bangladesh. Euroasian J Hepato-Gastroenterol 2016; 6(1):1-4.
30. Mandal A, Bhattarai B, Kafle P, Khalid M, Jonnadula SK, Lamicchane J, et al. Elevated Liver Enzymes in Patients with Type 2 Diabetes Mellitus and Non-alcoholic Fatty Liver Disease. Cureus. 2018 Nov 23;10(11):e3626. doi: 10.7759/cureus.3626.
31. Arias F, Mancilla-Jimenez R. Hepatic fibrinogen de-posits in pre-eclampsia: immunofluorescent evidence. New England Journal of Medicine. 1976; 295(11):578-82.
32. Meltzer AA, Everhart JE. Association between diabe-tes and elevated serum alanine aminotransferase activity among Mexican Americans. American journal of epidemi-ology. 1997; 146(7):565-71.
33. Erbey JR, Silberman C, Lydick E. Prevalence of abnor-mal serum alanine aminotransferase levels in obese pa-tients and patients with type 2 diabetes. The American journal of medicine. 2000; 109(7):588-90.
34. Ghimire S, Shakya S, Shakya J, Acharya P, Pardhe BD (2018) Abnormal Liver Parameters among Individuals with Type 2 Diabetes Mellitus Nepalese Population. Biochem Pharmacol (Los Angel) 7: 243. doi: 10.4172/2167-0501.1000243
35. Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H, Kamps BS. Hepatology-A clinical textbook. Flying pub-lisher; 2014.
36. Jamaludin Mohamed, Nazratun Nafizah A. H., Zariyantey A. H., Budin S. B. Mechanisms of diabetes-induced liver damage: the role of oxidative stress and inflammation. Sultan Qaboos University Med J, 2016; 16(2): 132–141
37. Ayesha Nageen. The Biochemical Pattern of Liver Function Tests in Adult Patients of Diabetes and the Association with Hypoglycemic Medications. *Pak Armed Forces Med J* 2022; 72 (4): 1245-1248.
38. Miyake T, Kumagi T, Hirooka M, Furukawa S, Koizumi M, Tokumoto Y et al. Body mass index is the most useful predictive factor for the onset of nonalcoholic fatty liver disease: a community based retrospective longitudinal cohort study. *J. Gastroenterol.* 48, 413–22 (2013).
39. Arun J. Sanyal (2002). AGA technical review on nonalcoholic fatty liver disease. , 123(5), 1705–1725. doi:10.1053/gast.2002.36572
40. Loomis AK, Kabadi S, Preiss D, Hyde C, Bonato V, St Louis M et al. Body Mass Index and Risk of Nonalcoholic Fatty Liver Disease: Two Electronic Health Record Prospective Studies. *J. Clin. Endocrinol. Metab.* 101, 945–52 (2016).
41. Wolf AM, Busch B, Kuhlmann HW, Beisiegel U. Histological changes in the liver of morbidly obese patients: Correlation with metabolic parameters. Obes Surg 2005; 15:228-37.
42. Han N, Htoo H, Kyaw S, Htet A. Determinants of Abnormal Liver Function Tests in Diabetes Patients in Myanmar. International Journal of Diabetes Research. 2012;1(1):36-41
43. Nadu D. Prevalence of abnormal liver function tests in Type 2 DM .Journal of Diabetes Research. 2015,5(1),31-8
44. Rui F, Jufang W, Jinman D. Association between body mass index and fatty liver, Journal of Scientific reports. 2018;8 (15273):33419-6
45. Morling J, Strachan M, Hayes P, Butcher I, Frier B, Reynolds R, et al. Prevalence of abnormal plasma liver enzymes in older people with Type 2 diabetes. Diabetic medicine. 2012; 29 (4):488-91.
46. Giandalia A, Romeo EL, Ruffo MC, Muscianisi M, Gior-gianni L, Forte F, et al. Clinical correlates of persistently elevated liver enzymes in type 2 diabetic outpatients. Pri-mary care diabetes. 2017; 11(3):226-32.
47. Kalas MA, Chavez L, Leon M, Taweesedt PT, Surani S. Abnormal liver enzymes: A review for clinicians. *World J Hepatol* 2021; 13(11): 1688-1698